1. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Adjei and Waldrep et al., in view of Gilbert, Knight et al. and Applicant's admission on the record. According to the Examiner Adjei, Waldrep, Gilbert, Knight and Applicant admit on the record that the claimed compounds are old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. According to the Examiner, these medicaments are thought as useful for treating graft rejection, inflammation and those conditions claimed and disclosed by Applicant.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the difference between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S.1, (1996). The Court of Appeals for the Federal Circuit (CAFC) summarized the legal standard with regard to the showing necessary to support a proper rejection under Section 103 in *In re Rijckaert*, 28 USPQ2d 1955, (1993) as follows:

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness....A *prima facie* case of obviousness is established when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. If the Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned. Id. (citations omitted).

The prior art relied upon by an examiner to establish a *prima facie* case must not only suggest that the claimed device or composition be made or that a claimed method be performed, but the prior art must also provide one of ordinary skill in the art with a reasonable expectation that the claimed subject matter can be successfully used to effect a practical purpose .

In re Vaeck 20 USPQ2d 1438, 1442 (Fed. Cir. 1991): Thus, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In *re: O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Circ. 1988).

In the present instance, the relevant inquiry is whether any of the cited references suggest compositions of non-encapsulated aerosolized cyclosporine and their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders.

A review of the Waldrep, Gilbert and Knight references reveals that each of the references only disclose compositions comprising liposomal encapsulated cyclosporine. None of the references suggest compositions of non-encapsulated cyclosporine much less their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. In addition, although Adjei discloses compositions of non-encapsulated cyclosporine, Adjei fails to disclose or suggest that such non-encapsulated compositions could be successfully used to prevent graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions.

Applicant asserts that the mere disclosure of liposomal formulations of cyclosporine would not only fail to suggest the claimed methods and compositions of the invention, *i.e.*, non-encapsulated formulations of cyclosporine, but also fail to provide any expectation that the claimed methods utilizing such compositions could successfully be practiced. This is because one of ordinary skill in the art would recognize that liposomal formulations containing cyclosporine would have altered pharmacokinetic properties, such as

biodistribution, clearance rates, and toxicity as compared to non-encapsulated formulations of cyclosporine since a lipid membrane surrounds the active drug product resulting in hydrophobic and hydrophilic aerosol droplet interactions.

In addition, a number of references seem to teach away from the use of non-encapsulated formulations of cyclosporine....a further indicia of non-obviousness. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F. 2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986). For example, Knight states in column 2, lines 5-7 that "in laboratory animals the use of liposomes actually reduced toxic effects observed with the drug alone." Furthermore, as set forth in Gilbert (1996, J. of Aerosol Medicine 9:111-122: Exhibit A), "incorporation of potentially useful drugs into liposomes instead of using free drug has several advantages: solubility of lipophilic drugs allows for much greater concentrations of drug to be used; in many cases, incorporation decreases a drug's toxicity without affecting its inhibitory effects, and liposomal formulations may lead to better pharmacokinetics such that shorter and/or fewer treatments are necessary."

However, despite this teaching away, Applicants have demonstrated, unexpectedly, that doses of non-encapsulated cyclosporine as high as 300 mg per day are tolerated by the treated patient as demonstrated by the working examples presented in the specification (Example 6, p.22-28 of the specification).

Furthermore, Applicant maintains that there are a number of potential drawbacks associated with the use of liposomal encapsulated formulations of cyclosporine that can be avoided by the use of the non-encapsulated cyclosporine compositions of the invention. For example, the Examiner's attention is invited to pg.1573 of Harrington et al., (2002, Journal of Pharmacy and Pharmacology 54:1573; Exhibit B) which states the following:

> "Formidable difficulties were presented by the need to produce stable drug-containing liposomes in a reliable, reproducible way. The entrapment conditions for any particular agent need to be optimized individually. Because liposomes can carry drugs in three compartments (water-soluble agents in the central aqueous core, lipid-soluble agents in the membrane, peptides and small proteins at the lipid-aqueous interface), a diverse range of optimal encapsulation conditions may exist for different agents. In addition, the release kinetics of the entrapped agents can vary, depending on the liposomal formulation, and this can effect the therapeutic efficacy. Therefore, development of agents for preclinical and clinical uses can be both laborious and expensive."

Furthermore, the results presented in Bridges et al, (2000, International Journal of Pharmaceutics 204:69-79: Exhibit C) demonstrate that selection of both nebulizer and liposome components of the nebulizer-liposome system are critical for drug delivery to the respiratory lung regions. Finally, as set forth in Desai et al. (2003, Pharmaceutical Research 20:442; Exhibit D), it was established that the encapsulation of polymyxin B sulfate, typically a systemic antibiotic, into liposomes reduced its antimicrobial activity indicating that encapsulation of a therapeutic agent into lipsomes can effect the efficacy of the agent.

In summary, Adjei and Waldrep, in combination with Gilbert and Knight, fail to suggest the compositions of the claimed invention or provide a reasonable expectation of success in the use of such compositions for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. Furthermore, the non-encapsulated cyclosporine of the invention provides compositons and methods for treating pulmonary disorders without the need for optimization of encapsulation conditions. Applicants respectfully request, therefore, that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicant believes that the invention described and defined by the claims is patentable. Withdrawal of all rejections and consideration of the new claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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